OIPE JC152 JAN 15 2002 PATENT & TRADEMARK OFFICE

FULBRIGHT & JAWORSKI L.L.P.
A REGISTERED LIMITED LIABILITY PARTNERSHIP
600 CONGRESS AVENUE, SUITE 2400
AUSTIN, TEXAS 78701

TELEPHONE: 512/474-5201
FACSIMILE: 512/536-4598

MARK B. WILSON
PARTNER

INTERNET ADDRESS:
MBWILSON@FULBRIGHT.COM

DIRECT DIAL: 512/536-3035

HOUSTON
WASHINGTON, D.C.
AUSTIN
SAN ANTONIO
DALLAS
NEW YORK
LOS ANGELES
MINNEAPOLIS
LONDON
HONG KONG

AF/1600
TECHNOLOGY CENTER 1600/2900
JAN 17 2002
RECEIVED

November 2, 2001

FILE: UTSD:553
10017634

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on the date below:

November 2, 2001
Date

Mark B. Wilson

BOX AF
Commissioner for Patents
Washington, DC 20231

RE: *SN 09/339,352 "ABSORPTIVE HYPERCALCIURIA LOCUS ON CHROMOSOME 1" - Berenice Y. Reed-Gitomer & Charles Y.C. Pak (Client Ref. UTSMC/DAL:553)*

Sir:

Please find enclosed:

1. Response to Notification of Non-Compliance with 37 C.F.R. § 1.192(c) and Submission of Substitute Appeal Brief;

2. Substitute Appeal Brief (original and 2 copies), with Appendices A and B;

3. A return postcard to acknowledge receipt of these materials. Please date stamp and mail this postcard.

It is believed that no fees under 37 C.F.R. §§ 1.16 to 1.21 are occasioned by the filing of this paper, however, should the Commissioner determine otherwise, the Commissioner is hereby authorized to deduct said fees from Fulbright & Jaworski Deposit Account No. 50-1212/10017634/MBW.

Respectfully submitted,

Mark B. Wilson
Reg. No. 37,259

MBW:plm
Encl.

OIPE JC162 JAN 15 2002 PATENT & TRADEMARK OFFICE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Berenice Y. Reed-Gitomer
Charles Y.C. Pak

Serial No.: 09/339,352

Filed: June 23, 1999

For: ABSORPTIVE HYPERCALCIURIA LOCUS ON CHROMOSOME 1

Group Art Unit: 1653

Examiner: H. Robinson

Atty. Dkt. No.: UTSD:553/MBW

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

November 2, 2001
Date

Mark B. Wilson

SUBSTITUTE APPEAL BRIEF

OIPE JC152 JAN 15 2002 PATENT & TRADEMARK OFFICE

TABLE OF CONTENTS

OIPE JC152
JAN 15 2002
PATENT & TRADEMARK OFFICE

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Berenice Y. Reed-Gitomer
Charles Y.C. Pak

Serial No.: 09/339,352

Filed: June 23, 1999

For: ABSORPTIVE HYPERCALCIURIA LOCUS ON CHROMOSOME 1

Group Art Unit: 1653

Examiner: H. Robinson

Atty. Dkt. No.: UTSD:553/MBW

SUBSTITUTE APPEAL BRIEF

BOX AF
Commissioner of Patents
Washington, D.C. 20231

Sir:

Appellants hereby submit an original and two copies of this substitute Appeal Brief to the Board of Patent Appeals and Interferences in response to the final Office Action dated November 7, 2000. The Notification of Non-Compliance with 37 C.F.R. 1.192(c) was mailed on October 2, 2001, thus making this substitute Appeal Brief due on November 2, 2001. The fee for filing the Appeal Brief has been previously paid. Should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed material, the Commissioner is authorized to deduct said fees from or to Fulbright & Jaworski L.L.P. Account No.: 50-1212/10017634/MBW.

STATEMENT OF SUBSTANCE OF INTERVIEW PURSUANT TO 37 C.F.R. § 1.133(b)

Appellants hereby submits a statement of the substance of the telephone interview with Examiner Robinson on September 27, 2001, pursuant to 37 C.F.R. § 1.133(b). Examiner Robinson telephoned Mark B. Wilson, Appellants' representative, to clarify issues raised in the Appeal brief filed July 16, 2001. Mr. Wilson was unavailable. Mr. Wilson returned the phone call and was informed by Examiner Robinson that the issues were resolved. Mr. Wilson inquired as to what decisions were made based on the response filed. Examiner Robinson informed Mr. Wilson that a Notice of Non-Compliance with 37 C.F.R. § 1.192(c) would be issued. Mr. Wilson indicated that based on the finding of non-compliance he would consider responding with an appeal brief that would set forth why each claim is separately patentable.

I. REAL PARTY IN INTEREST

The real party in interest is the assignee, Board of Regents, The University of Texas System, Austin, Texas.

II. RELATED APPEALS AND INTERFERENCES

There are no interferences or appeals for related cases.

III. STATUS OF THE CLAIMS

Claims 1-26 were originally filed in the present application. During prosecution, claims 8-9, 16 and 18-26 were cancelled and claims 1, 10, 11 and 12 were amended. Accordingly, claims 1-7, 10-15 and 17 are pending. Of these, claims 1-7, 10-15 and 17 are the subject of the present appeal and stand appealed. A copy of the appealed claims is attached as Appendix A to this Brief.

IV. STATUS OF AMENDMENTS

Appellants have made no amendments subsequent to the final rejection.

V. SUMMARY OF THE INVENTION

This invention involves Appellants' discovery of an area on human chromosome 1 that is genetically linked to hypercalciuria in general and absorptive hypercalciuria in specific. *See* Specification, p. 5, lns. 27-30, p. 6, lns. 1-15. The specific area of chromosome 1 involved in the invention is that region containing 1q23 and 1q24. *See* Specification, p. 6, lns. 12-30. This discovery allows one to screen subjects and determine if the subject has an increased risk of absorptive hypercalciuria. The screening methods generally comprise obtaining a sample of nucleic acid from a subject and analyzing the sample of nucleic acid to detect the presence or absence of a genetic mutation in the genomic region of chromosome 1. The presence of such a mutation indicated in increased risk of hypercalciuria; the absence of such a mutation does not indicate an increased risk. *See* Specification, p. 6, lns. 11-19. The nucleic acid can be analyzed using standard techniques well known and used by those of ordinary skill in the art, for example, PCR, diagnostic RFLP analysis, RNase protection assay or RNase mismatch cleavage.

VI. ISSUES ON APPEAL

The issues for the Board's consideration are:

Whether claims 1-7, 10-15 and 17 are properly rejected under 35 U.S.C. § 101 as lacking a specific and substantial asserted utility or a well established utility.

Whether claims 1-7, 10-15 and 17 are properly rejected under 35 U.S.C. § 112, first paragraph, as lacking a specific utility to enable one skilled in the art to use the claimed invention without undue experimentation.

Whether claims 1-7, 10-15 and 17 are properly rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter with Appellant regards as the invention.

VII. GROUPING OF THE CLAIMS

For purposes of this Appeal, the claims should stand or fall separately, as described below.

For the purpose of the rejection under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, claim 2 should stand or fall separately from the remainder of the claims. Claim 2 is directed specifically to the determination of whether or not an individual has an increased risk of developing absorptive hypercalciuria, instead of hypercalciuria of any form. The majority of the data in the specification and the Declaration of Charles Y.C. Pak and Berenice Y. Reed-Gitomer, submitted as Appendix B herewith, relates specifically to an increased risk of absorptive hypercalciuria. These data are discussed below. Therefore, although Applicants submit that such a determination would not be supported by the facts of this case, the Board could determine that a claim of the scope of present claim 1 is properly rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, while a claim limited in scope to absorptive hypercalciuria is not properly rejected under these grounds.

VIII. ARGUMENT

A. Claim 1 Has an Asserted Utility

The Action rejects claim 1 under 35 U.S.C. §101 asserting that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility based on screening for increased risk of developing hypercalciuria." The Examiner contends that the specification does not clearly set forth how a standardized screening method would be

developed to screen for increased risk of absorptive hypercalciuria (AH). The Examiner also contends that the uncertainty of the gene region and variability of the mutation, may be indicia of a "real world" use, but in view of the absence in the application of working examples and complete details for carrying out the processes indicated in the claims, the utility indicated would require further experimentation. Appellants traverse this rejection.

1. Asserted Utility Creates Presumption of Utility

The Manual of Patent Examining Procedure (MPEP) sets forth the guidelines for compliance with the utility requirement of 35 U.S.C. § 101 in MPEP § 706.3(a)(1). Subsection (B)(1) makes it clear that an invention has utility if a particular purpose (*i.e.* "specific utility") is asserted by the specification and a person of ordinary skill would consider this assertion credible. Both the Federal Circuit Court and the Court of Customs and Patent Appeals have directed the Patent Office to presume that an Applicant's assertion of utility is true and is sufficient to satisfy the utility requirement of 35 U.S.C. §101. *See* e.g., *In re Jolles*, 628 F.2d 1322, 206 USPQ (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (CCPA 1965); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA); *In re Sichert*, 556 F.2d 1154, 1159, 196 USPQ 209-212-13 (CCPA 1977).

Appellants have clearly asserted the utility of the claimed invention. The specification at page 6, lines 11-15, states that: "[d]escribed in this invention is a method for screening for an increased risk of hypercalciuria by obtaining a sample nucleic acid from a subject; and analyzing the sample nucleic acid to detect the presence or absence of a genetic mutation in genomic region associated with an increased risk of developing hypercalciuria." The specific utility asserted by the application is thus the use of the claimed locus in screening for an increased risk of developing hypercalciuria. A person of ordinary skill would find this a credible assertion. The

instant invention sets forth a genetic locus that is statistically related to an absorptive hypercalciuria (AH) phenotype in the screened kindred groups. The detection of the altered loci would determine an individual at risk and would facilitate early detection of disease onset and potential intervention to allow for modifications in lifestyle or diet that could prevent or delay onset of the disease.

Any contention of a "*lack of asserted utility*" simply does not withstand an examination of the facts. The specification clearly discloses a specific genomic region of chromosome 1, 1q23.3-1q24, that is reasonably correlated to a specific disease condition, hypercalciuria, in particular absorptive hypercalciuria (AH). The inventors established a statistically significant linkage between an alteration in this loci and the AH phenotype. The asserted utility of the present invention falls within the guidelines established by the MPEP governing utility of applications. *See* MPEP § 2107.

2. The Asserted Utility Is Understood by Those of Skill in the Art and Does not Require Undue Experimentation

A person of ordinary skill will recognize that the instant invention provides substantive evidence that localizes a disease susceptibility phenotype to a specific genetic locus.

Localization of mutations in a genetic locus requires the practice of simple screening processes. Such screening process are well-known to those of skill in the art and are described in great detail in the specification. For example the specification teaches nucleic acid based screening assays at pg. 45, ln. 7, to pg 60, ln. 20. Further, Example 3 of the specification teaches techniques shown by the inventors to allow the determination as to whether there is a mutation in the 1q23.3-1q24 region, at pg. 124, ln. 20, to pg. 126, ln. 7. Example 4 of the specification teaches a typical technique that may be used to identify individuals at risk from hypercalciurea, at pg. 126, ln. 9, to pg. 127, ln. 19. Example 5 describes some specific genetic mutations that are

linked to hypercalciuria, which were determined using the techniques disclosed in the specification, pg. 127, ln. 21, to pg. 128, ln. 28.

In addition to the data contained in the specification, which was available at the time the application was filed, the Inventors have now obtained even more data that support that mutations in the 1q23.3-1q24 region are indicative of an increased risk for hypercalciurea. Attached as Exhibit A is a Declaration of Charles Y.C. Pak and Berenice Y. Reed-Gitomer. Drs. Pak and Reed-Gitomer are the inventors of this application.

In their Declaration, Drs. Pak and Reed-Gitomer set forth that the present claims are based on the inventors' discovery that an area on human chromosome 1, 1q23.3-1q24 is linked to absorptive hypercalciuria (AH). The claims relate to methods allowing for the determination as to whether an individual has a genetic predisposition for hypercalciurea. Exhibit A, ¶3. They set forth known techniques described in the specification that may be used to screen for mutations in the 1q23.3-1q24 region. For example, they cite to pg. 45, ln. 7, to pg 60, ln. 20, pg. 124, ln. 20, to pg. 126, ln. 7, pg. 126, ln. 9, to pg. 127, ln. 19, and pg. 127, ln. 21, to pg. 128, ln. 28 of the specification for the teaching of such techniques, their use in the context of the invention, and results supporting the utility of the claimed methods. Exhibit A, ¶4.

With their Declaration, the inventors submit new data which have been obtained with these techniques. These data confirm that the presence of a mutation in one or both alleles of 1q23.3-1q24 is associated with a significant increase in estimated risk for the occurrence of the AH phenotype. The new data are included and discussed in detail in a manuscript attached to the Declaration a Exhibit 1. Exhibit A, ¶5.

These new data are even further evidence that the claimed methods of analyzing sample nucleic acid to detect the presence or absence of a genetic mutation in the genomic region of

1q23.3-1q24 allow for the determination of whether one has a genetic predisposition for AH. Specifically, the data show that screening of genomic DNA from 16 subjects revealed 6 base changes in 1q23.3-1q24. Four of six base changes found in 1q23.3-1q24 were shown to indicate a significant increase in the relative risk for AH. For one of the base changes, it was not possible to calculate a risk odds ratio, because the control population was found to contain no mutant alleles. One base change was found to have a non-significant odds ratio. Exhibit A, ¶¶6-8.

In view of these new data, the apparent suggestion of the Action that the claimed invention lacks utility because it is not possible to know which mutations that may be found in the 1q23.3-1q24 region are linked to an increased risk of hypercalciurea is simply not the case. As shown in the data in the specification and the Declaration of Drs. Pak and Reed-Gitomer, the occurrence of mutations in the 1q23.3-1q24 region is correlated with the increased risk of hypercalciurea. This correlation does not appear limited to a single or small subset of mutations. In fact, most such mutations thus far found have been found to be indicative in a significantly increased risk of AH. Exhibit A, ¶9.

The apparent suggestion of the Action that the invention only has utility for and is only enabled in regard to the detection of specific mutations listed in the specification is not correct. Rather, Applicants have shown that having a mutation in the 1q23.3-1q24 region is statistically correlated to an increased risk of hypercalciurea. The present invention is not limited to cases where a subject is diagnosed as positively having hypercalciurea. Rather, it encompasses all instances where one screens for a mutation in the 1q23.3-1q24 region, and thereby, determines whether or not the subject has a increased risk of developing hypercalciurea

Based on the data in the specification and their Declaration, the Applicants have declared that, "[b]y following the teachings of the specification and employing the methods taught in the

specification and known to those of skill in molecular biology, skilled molecular biologists will recognize that they can practice the claimed invention and determine whether a subject has a mutation in the 1q23.3-1q24 region, and thereby, determine whether or not the subject has a increased risk of developing hypercalciurea." Exhibit A, ¶10. Drs. Pak and Reed-Gitomer further state that, in view of the data in the specification and the additional data supplied in Table 1, the invention as claimed has utility and is enabled by the specification such that one of skill in the art would know how to use the present invention. Exhibit A, ¶11.

Therefore it would not require undue experimentation to perform similar screening on individuals at risk for AH using methods similar to those set forth in the specification but restricted to the claimed loci. In its simplest embodiment, the instant invention may be carried out by performing screening procedures similar to those used for detecting the initial loci. In addition, a person of ordinary skill would be aware of more refined methods to screen for chromosomal deletions, alterations or other mutations.

The Examiner's mere contention that it would be undue experimentation due to the absence of data is merely speculation by the Examiner. The Examiner appears to assert more knowledge than the skilled artisans and thus, is substituting her judgment for that of an established expert in the art. This is improper. *In re Zeidler*, 682 F.2d.961, 966-967 (Fed. Cir. 1982). Appellants assert that the Office must provide specific, evidentiary scientific basis (e.g., scientific journal articles, or excepts form patents or scientific treatises) for its factual conclusions that the present invention "lacks an asserted utility".

Therefore, in view of the arguments that one of skill in the art would reasonably recognize a correlation between the asserted utility and the ability to screen for AH as the instant

specification sets forth, Appellants respectfully request that the Board overturn the rejection of the claims for "lack of utility."

B. Claim 1 Is Enabled

The Action rejects claim 1 under 35 U.S.C. 112, first paragraph, asserting that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility" and thus a person of ordinary skill would not know how to use the invention without undue experimentation. In the Action, the Examiner also reinstated her contentions that the specification is not enabled for one skilled in the art to make and use the claimed invention. The Action contends that the claimed invention is enabled for the nucleic acid sequence of SEQ ID NO: 1 that encodes a protein contained in SEQ ID NO:2, however, does not provide enablement for any hypercalciuria gene nor a screening method for "increased risk" of AH. Appellants respectfully traverse this rejection.

As set forth above, the specification sets forth a screening method useful in detecting individuals potentially at risk for the development of hypercalciurea or a related phenotype. Thus, one of skill in the art would understand the utility of the invention as claimed.

A rejection based on a lack of enablement must be adequately supported by substantive evidence. The PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-370 (CCPA. 1971). The PTO must therefore provide reasons supported by the record as a whole of what the specification is not enabling. *Application of Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219-220 (CCPA 1979). Then and only then does the burden shift to the applicant to show that one of ordinary skill in the

art could have practiced the claimed invention without undue experimentation. *In re Strahilevitz*, 668 F.2d. 1229, 1232, 212 USPQ 561, 563-64 (CCPA 1982). [Emphasis added]

The Action has erroneously placed the burden of proof on the Appellants without offering any evidence or reasoning based on the record as a whole why the disclosure is not enabling for the pending claims. The single "grounds" of rejection is without support and is couched in terms that a person of ordinary skill would not be enabled to carry out the invention because one of ordinary skill would have no way of recognizing a utility for the invention. This is wrong.

The instant specification sets forth a means for screening for hypercalciurea. Linkage analysis was performed in order to establish the correlation between the AH phenotype and the disclosed loci. A person of ordinary skill would understand that similar means to those taught by the specification could be employed to screen for the altered loci in other individuals deemed to be at risk for the development of the disease, *i.e.*, based on family history, as the specification teaches a successful means of screening (*see* examples 1 and 2). If the rejection is to be maintained under §112, the Examiner must support the noted position by citing published references or by Examiner's Affidavit, as required by MPEP 2144.03.

No undue experimentation is needed to practice the invention, because Appellants' disclosure clearly enables a screening method for determining an individual with an "increased risk" of the AH phenotype. A person of ordinary skill could readily develop methods of screening for defects within the disclosed region.

Appellants provide sufficient evidence that inherited hypercalciuria is, in some individuals, linked to an inherited defect in the 1q23.3-1q24 region of chromosome 1. *See* Specification, page 130, Table 7. The Appellants successfully established, through linkage

analysis, that a genetic defect (*e.g.*, specific mutations) exhibited by three unrelated, effected kindred localized to the q arm of chromosome 1 at 1q23.3q-q24. Based upon this information, it would not require undue experimentation to derive a means of screening individuals for an increased risk of AH based upon a similar genetic defect. Techniques would clearly be within the purview of a person of ordinary skill to readily develop screening techniques based upon this disclosure for determining whether individuals are genetically predisposed to developing AH. Further, the specification provides teaching related to how such methods could be derived including means of eliciting specific defects within the region (*See*, for example, pg. 58, ln. 20 *et. seq*) as well as sequence information for areas within the disclosed region (*See*, for example, SEQ ID NOs. 1-11). One of ordinary skill would recognize that the disclosure provides adequate information such that assays could be developed employing techniques to detect specific inherited defects indicative of a genetic predisposition for AH (for example, RNase protection or DGGE as discussed in the specification at pg. 58 ln. 20 *et. seq.*).

Appellants do not appreciate that the Action asserts that the working example of Example 5 (*See* Specification, pages 127-131) is inadequate. An application need not include working examples in order to be enabled. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA). The fact that the Application provides a working example that correlates specific mutations located in the chromosome 1q24 locus to the AH phenotype should not be dismissed for being inadequate. Based upon the knowledge of one of ordinary skill in the relevant art and the guidance provided in the present Application, it would not require undue experimentation to use the loci and sequence information provided by the Appellants to screen for specific defects within the 1q23.3q-q24 region of chromosome 1 and correlate the presence of a genetic defect as a predictor of increased risk for the AH phenotype.

Further, as discussed above, the inventors have submitted, in the form of a declaration, new data that even further establish the utility and enablement of the invention.

In view of the above, Appellants request that the Board overturn the enablement rejection.

C. Claim 1 Is Definite

The Action rejects claim 1 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Appellants regard as the invention. Claim 1 is deemed indefinite by the Action because "species (a) does not define what mutation is being detected [and] [f]urthermore, it is unclear how species (b) relates to an increased risk." The Action further finds the claim indefinite because of the amendatory language previously submitted and because it is not demonstrated where the mutation causes increased risk. Appellants respectfully traverse.

Appellants submit that the standard being applied by the Action is improper. In order to satisfy the requirements of definiteness under §112, a claim, read in light of the specification, must reasonably apprise those of skill in the art of its scope. *See Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 1217, 18 USPQ2d 1016, 1030 (Fed.Cir.). The specification sets forth a standard means for successfully detecting the altered loci linked to the hypercalciurea susceptibility phenotype, the specific mutated sequence is not necessarily relevant to the elucidation of an indicator of hypercalciurea. Linkage analysis successfully determined an altered loci linked to hypercalciurea. This, in and of itself, has utility in screening for hypercalciurea susceptibility. While a "mutation" is obviously the basis of the detected chromosomal alteration, elucidation of the specific nucleotide change is not, at this point, necessarily pertinent to the ability to successfully screen for the change. Nevertheless, the

screening method that successfully detected the chromosomal change by linkage analysis is a "mutation" and thus the term is employed properly in the claim.

The Action apparently seeks to require that the specification set forth the exact mutated sequence that leads to the development of hypercalciurea. This requirement is, however, not the threshold for patentability and is unnecessary to properly execute the invention within the scope of the claim. The specification sets forth a basic methodology for detecting the altered loci. One of ordinary skill would further recognize that a variety of commonly practiced screening procedures could be carried out to detect hypercalciurea susceptibility based upon the recognition of the significance of the disclosed loci. Furthermore, based upon the derivation of the role of the disclosed loci, it would not require undue experimentation nor any inventive input to detect specific mutated sequences within the disclosed loci that might further relate to the development of hypercalciurea. This is demonstrated by the new data submitted in the Declaration of Drs. Pak and Reed-Gitomer, which confirm that the methods of the specification are useful to detect a risk of hypercalciurea.

In light of the above arguments, the Board should overturn this rejection.

D. Claim 2 is Separately Patentable over all Rejections

1. Claim 2 Has an Asserted Utility for Additional Reasons

In addition to the above arguments, which apply to all of the claims, Applicants further assert that the subject matter of current claim 2 has utility for even additional reasons. Claim 2 is directed specifically to determining whether or not one has an increased risk of absorptive hypercalciurea, the specific form of hypercalciurea about which the inventors have gathered the most information. Although Appellants submit that they have shown that the invention has utility in regard to determining whether or not one has an increased risk of hypercalciurea in

general, it is possible that the Board could disagree with this broad of a utility. However, Appellants submit that there are additional and compelling arguments for the utility of the subject matter of claim 2, since all of the mutations which have been found to result in hypercalciurea have also been specifically linked to absorptive hypercalciurea. Therefore, even if the Board does not find the subject matter of claim 1 to have utility, the subject matter of claim 2 should be found to have utility.

In view of the above, Appellants request that the Board overturn the utility rejection for claim 2.

2. Claim 2 is Enabled for Additional Reasons

In addition to the above arguments, which apply to all of the claims, Applicants further assert that the subject matter of current claim 2 is enabled for even additional reasons. Claim 2 is directed specifically to determining whether or not one has an increased risk of absorptive hypercalciurea, the specific form of hypercalciurea about which the inventors have gathered the most information. Although Appellants submit that they have shown that the invention is enabled in regard to determining whether or not one has an increased risk of hypercalciurea in general, it is possible that the Board could disagree with this broad of enablement. However, Appellants submit that there are additional and compelling arguments for the enablement of the subject matter of claim 2, since all of the mutations which have been found to result in hypercalciurea have also been specifically linked to absorptive hypercalciurea. Therefore, even if the Board does not find the subject matter of claim 1 to be enabled, the subject matter of claim 2 should be found to be enabled.

In view of the above, Appellants request that the Board overturn the enablement rejection for claim 2.

E. The Application Should Receive the Provisional Filing Date

The Action asserts that the Appellants have "not complied with one or more conditions for receiving the benefit of an earlier filing date." The Action contends that the application will be provided with the filing date of the present application because "the Examiner read the provisional application and did not find support for sequences recited in the claims and disclosed in the specification" and "the marker D1S2681 wherein the genomic region of the invention is comprised." Appellants respectfully traverse this allegation.

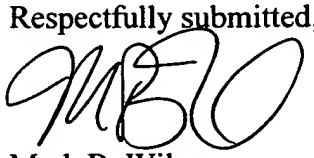
Appellants note that, as no prior art has been cited against the instant application, receiving the provisional filing date is not relevant to the present appeal. Nevertheless, Appellants submit that, while additional material was provided when the provisional application was converted to the instant application, it is nevertheless improper to assert that the full scope of the claims as currently pending were not taught by the original provisional application. Claim scope that is enabled by the initial provisional application should be accorded the earlier filing date under the requirements of 35 U.S.C. § 119(e). For example, claim 1 includes the limitation "said genomic region is comprised in chromosome 1q23.3-1q24" but does not limit the loci to D1S2681. The chromosomal region 1q23.3-1q24 as claimed is properly designated in the provisional application. Therefore, as the claim scope applies to this limitation, the earlier filing date is proper.

IX. CONCLUSION

Appellants have provided arguments that overcome the pending rejections. Appellant respectfully submits that the Action's conclusions that the claims should be rejected are unwarranted. It is therefore requested that the Board overturn the Action's rejections.

Please date stamp and return the enclosed postcard to evidence receipt of this document.

Respectfully submitted,



Mark B. Wilson
Reg. No. 37,259
Attorney for Appellants

FULBRIGHT & JAWORSKI L.L.P
600 Congress Avenue, Suite 2400
Austin, Texas 78701
512.536.3035 (voice)
512.536.4598 (fax)

Date: November 2, 2001

A

This Page Blank (uspto)

APPENDIX A: Claims on Appeal

1. A method for screening for an increased risk of hypercalciuria comprising:
   (a) obtaining a sample nucleic acid from a subject; and
   (b) analyzing the sample nucleic acid to detect the presence or absence of a genetic mutation in genomic region associated with an increased risk of developing hypercalciuria, wherein said genomic region is comprised in chromosome 1q23.3-1q24.

2. The method of claim 1, wherein the hypercalciuria is further defined as absorptive hypercalciuria.

3. The method of claim 1, wherein the hypercalciuria is further defined as osteoporosis with hypercalciuria.

4. The method of claim 3, wherein the osteoporosis with hypercalciuria is further defined as idiopathic osteoporosis with hypercalciuria.

5. The method of claim 3, wherein the osteoporosis with hypercalciuria is further defined as postmenopausal osteoporosis with hypercalciuria.

6. The method of claim 1, wherein the nucleic acid is DNA.

7. The method of claim 1, wherein the subject is a human.

10. The method of claim 1, wherein the genomic region is located between markers D1S2681 and D1S2815.

11. The method of claim 1, wherein the genomic region has a sequence contained in SEQ ID NO:1.

12. The method of claim 1, wherein the genomic region has a sequence contained in at least one genetic sequence selected from the group consisting of the genetic sequences set forth in GenBank Accession # Z97876, (SEQ ID NO: 7 SEQ ID NO: 8 and SEQ ID NO: 9), GenBank Accession # Z99943 (SEQ ID NO: 10), and GenBank Accession # AL031733 (SEQ ID NO: 7).

13. The method of claim 1, wherein the genomic region has a lod score of greater than 3.0 but less than 30.0.

14. The method of claim 1, wherein analyzing the sample nucleic acid is done with a PCR procedure, diagnostic RFLP analysis, RNase protection assay, or RNase mismatch cleavage assay.

15. The method of claim 14, wherein analyzing the sample nucleic acid is done with a PCR procedure.

17. The method of claim 15, wherein the screening for an increased risk of hypercalciuria comprises:

(a) obtaining a sample nucleic acid from a subject; and

(b) analyzing the sample nucleic acid to detect the presence or absence of a genetic mutation in genomic region associated with an increased risk of developing hypercalciuria.

B

This Page Blank (uspto)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Berenice Y. Reed-Gitomer Charles Y.C. Pak	Group Art Unit: 1653
Serial No.: 09/339,352	Examiner: H. Robinson
Filed: June 23, 1999	Atty. Dkt. No.: UTSD:553/MBW
For: ABSORPTIVE HYPERCALCIURIA LOCUS ON CHROMOSOME 1	

DECLARATION OF CHARLES Y.C. PAK AND BERENICE Y. REED-GITOMER UNDER 37 U.S.C.§ 1.132

We, Charles Y.C. Pak and Berenice Y. Reed-Gitomer, do hereby declare and state the following:

1. We are both professors at the Center for Mineral Metabolism & Clinical Research at the University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, and inventors of the above referenced application.

2. We have read the above-captioned patent application, as well as the Official Actions and Responses to Official Actions in this case.

3. The present claims are based on our discovery that an area on human chromosome 1, specifically that area including 1q23.3 and 1q24, is linked to absorptive hypercalciuria ("AH"). The claims relate to methods allowing for the determination as to whether an individual has a genetic predisposition for hypercalciuria. The claimed methods comprise obtaining a sample of nucleic acid from a subject and analyzing the sample of nucleic acid to detect the presence or absence of a genetic mutation in the

genomic region of 1q23.3 and 1q24. The data obtained from the screening methods can be analyzed using standard statistical calculations to determine an increased risk of the AH phenotype.

4. Known techniques may be used to screen for mutations in the 1q23.3-1q24 region. These techniques are described in the patent specification. For example, the specification teaches nucleic acid based screening assays at pg. 45, ln. 7, to pg 60, ln. 20. Further, Example 3 of the specification teaches techniques that allow the determination as to whether there is a mutation in the 1q23.3-1q24 region, at pg. 124, ln. 20, to pg. 126, ln. 7. Example 4 of the specification teaches a typical technique that we have used to identify individuals at risk from hypercalciuria, at pg. 126, ln. 9, to pg. 127, ln. 19. Example 5 describes some specific genetic mutations that are linked to hypercalciuria, which were determined using techniques disclosed in the specification, pg. 127, ln. 21, to pg. 128, ln. 28. This is confirmed by additional data we have obtained, which is discussed below.

5. Since the time of filing of the application, these techniques, were recently used to screen additional individuals for the presence or absence of mutations in 1q23.3-1q24 and determine the increased risk of AH occurrence. The presence of a mutation in one or both alleles of 1q23.3-1q24 was associated with a significant increase in estimated risk for the occurrence of the AH phenotype. The new data supporting this are included in the manuscript attached hereto as Exhibit 1.

6. The data in Exhibit 1 are even further evidence that the claimed methods of analyzing sample nucleic acid to detect the presence or absence of a genetic mutation in

the genomic region of 1q23.3-1q24 allow for the determination of whether one has a genetic predisposition for AH.

7. Exhibit 1 reports that screening of genomic DNA from 16 subjects revealed 6 base changes in 1q23.3-1q24.

8. As shown in Table 5 of Exhibit 1 and discussed in the text of Exhibit 1, four of six base changes found in 1q23.3-1q24 were shown to indicate a significant increase in the relative risk for AH. For one of the base changes, it was not possible to calculate a risk odds ratio, because the control population was found to contain no mutant alleles. One base change was found to have a non-significant odds ratio.

9. We understand that the Examiner in charge of this case has suggested that it is not possible to know which mutations that may be found in the 1q23.3-1q24 region are linked to an increased risk of hypercalciuria. This is not the case. As shown in the data in the specification and submitted herewith, the occurrence of mutations in the 1q23.3-1q24 region is correlated with the increased risk of hypercalciuria. This correlation does not appear limited to a single or small subset of mutations. In fact, most such mutations thus far found have been found to be indicative in a significantly increased risk of AH.

10. By following the teachings of the specification and employing the methods taught in the specification and known to those of skill in molecular biology, one can practice the claimed invention and determine whether a subject has a mutation in the 1q23.3-1q24 region, and thereby, determine whether or not the subject has an increased risk of developing hypercalciuria.

11. In view of the data in the specification and the additional data supplied in Table 1, the invention as claimed can be used to determine whether one has an increased risk of hypercalciuria and, further, the specification describes how to use the present invention to one skilled in molecular biology.

12. In view of the data in the specification and this declaration, skilled molecular biologists will recognize the utility of the presently claimed invention to determine whether one has an increased risk of hypercalciuria.

13. We hereby declare that all statements made herein on our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so make are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

July 9, 2001
Date

Charles Y.C. Pak

July 9 2001
Date

Berenice Y. Reed-Gitomer
Berenice Y. Reed-Gitomer